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This is a request for filing a Provisional Application for Patent under 37 CFR 1.53(c)

Inventor(s) and Residence(s) (city and either state or foreign country):

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Title: METHOD, SYSTEM, AND COMPUTER PROGRAM PRODUCT FOR PROCESSING OF SELF-MONITORING BLOOD GLUCOSE (SMBG) DATA TO ENHANCE DIABETIC SELF-MANAGEMENT

23 Sheets of specification.

_____ Sheets of drawings.

University of Virginia Patent Foundation claims small entity status as a nonprofit organization (37 CFR §§1.27(a)(3) and (c)). The Commissioner is hereby authorized to charge the Small Entity Fee of $80 to Deposit Account No. 50-0423.

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This invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. The government has certain rights in the invention.

YES ☒ NO ☐ Grant No. NIH/NIDDK: RO1 DK 28288 RO1 DK 51562

Dated: June 13, 2003

Respectfully submitted,

By: _____
Robert J. Decker (Reg. No. 44,056)

METHOD, SYSTEM, AND COMPUTER PROGRAM PRODUCT FOR PROCESSING OF SELF-MONITORING BLOOD GLUCOSE (SMBG) DATA TO ENHANCE DIABETIC SELF-MANAGEMENT

REPORT OF FINDINGS FROM PHASE 2 – PART 1:
Algorithm 1: Evaluation of HbA1c

CROSS-REFERENCES TO RELATED APPLICATIONS

The present invention is related to international patent application no. PCT/US01/09884 filed march 29, 2001 (Publication Nos. WO 01/72208 A2, WO 01/72208 A3), entitled "Method, System, and Computer Program Product for the Evaluation of Glycemic Control in Diabetes from Self-monitoring Data," and U.S. Patent Application Serial No.:10/240,228 filed September 26, 2002, entitled "Method, System, and Computer Program Product for the Evaluation of Glycemic Control in Diabetes from Self-monitoring Data," the entire disclosures of which are hereby incorporated by reference herein.

Table of Contents:

ABSTRACT

Background: This Phase 2 study validated and refined a previously presented to LifeScan (April, 2002) data analysis method that consists of three algorithms for evaluation of the two most important parameters of metabolic control in diabetes: HbA_{1c} and risk for hypoglycemia. This method uses routine self-monitoring blood glucose (SMBG) data and pertains directly to enhancement of home SMBG devices by introducing intelligent data interpretation logic, capable of predicting both HbA_{1c} and periods of increased risk for significant hypoglycemia. The method has two components: (1) **Algorithm 1** estimating HbA_{1c}, and (2) **Algorithms 2 & 3** predicting long-term and short-term (within 24 hours) significant hypoglycemia, respectively. In this report we describe the steps of development, optimization and validation of the HbA_{1c} estimation Algorithm 1, as well as its accuracy in estimating laboratory acquired HbA_{1c}.

Objective: The primary goal was to reach an accuracy of 95% of measurements within ±1 HbA_{1c} unit of a laboratory reference, which is the National Glycohemoglobin Standardization Program (NGSP) Criterion for accuracy for HbA_{1c} assays.

Methods:

Subjects: SMBG data was captured for 100 subjects with Type 1 and 100 subjects with Type 2 diabetes mellitus (T1DM, T2DM) for 6 months and 4 months respectively, with HbA_{1c} tests taken at months 0, 3 and 6 in T1DM and months 0, 2 and 4 in T2DM.

Development and Optimization of Algorithm 1: The Training Data Set consisted of SMBG and HbA_{1c} data collected up to month 3 for T1DM and up to month 2 for T2DM. These Training Data were used for optimization of Algorithm 1 and for evaluation of a number of *sample selection criteria* that would ensure better accuracy. The sample selection criteria are requirements for any SMBG sample collected by the meter, which, if met, ensure accurate estimation of HbA_{1c} from that sample. Consequently, the meter will scan every SMBG sample and if the sample selection criteria are met, will compute and display HbA_{1c} estimate. After analyzing various cut points the following criteria were selected:

1. *Test Frequency:* In order to generate an estimate of HbA_{1c}, the meter will require an average of 2.5 tests or more per day over the last 60 days, e.g. a total of 150 SMBG readings over the past two months. It is important to note that this is an average per day, testing every day is not required.
2. *Randomness of data:* Certain 60-day samples with only post-prandial testing, or insufficient nighttime tests (<3% of sample) are to be excluded. In addition a safeguard against highly concentrated testing at one modal time of day was incorporated. These criteria are described in detail in the report.

Results: Prospective Validation and Accuracy of Algorithm 1:
The algorithm, including the sample selection criteria, was then applied to Test Data Set 1, which included SMBG and HbA_{1c} data for two months prior to T1DM and T2DM subjects' last HbA_{1c}, and to an independent Test Data Set 2 consisting of 60 T1DM subjects who participated in a previous NIH study. The estimates obtained by Algorithm 1 were compared to reference HbA_{1c} levels for validation purposes. In Test Data Set 1 the algorithm reached the NGSP criteria with an *accuracy of 95.1%* within ±1 Hba_{1c} unit of the lab reference. In Test Data Set 2 the algorithm reached the NGSP criteria as well with an *accuracy of 95.5%* within ±1 Hba_{1c} unit of the lab reference. Investigation of the sample selection criteria showed that 72.5% of all subjects would generate such an accurate estimate every day, and 94% of all subjects would generate such an accurate an estimate about once every 5 days.

Conclusion: Routine SMBG data allow for accurate estimate of HbA_{1c} that meets the NGSP criterion for accuracy of *direct* HbA_{1c} assays.

Boris Kovatchev & Daniel Cox, University of Virginia

SUBJECTS & INCLUSION CRITERION

We have consented 100 subjects with Type 1 Diabetes (T1DM) and 100 subjects with Type 2 Diabetes (T2DM). One hundred seventy-nine subjects, 90 with T1DM and 89 with T2DM, completed significant portions of the SMBG data collection. The data of these 179 subjects were used for testing Algorithms 2 and 3. However, the testing of Algorithm 1 required that the subjects had not only SMBG data, but HbA_{1c} data *and* SMBG records taken in the 60 days prior to SMBG. At month 3 of this study (month 2 for T2DM), 153 subjects (78 with T1DM) had completed HbA_{1c} data and SMBG data meeting the above criterion. In addition, we used for testing of Algorithm 1 data for N=60 subjects with T1DM who participated in our previous NIH study (NIH). The demographic characteristics of all subjects are presented in Table 1.

Table 1: Demographic characteristics of the subjects.

Variable	T1DM	T2DM	NIH
Age (years)	41.5 (11.6)	50.9 (8.1)	44.3 (10.0)
Gender: % Male	41%	43%	46%
Duration of diabetes (years)	20.1 (10.1)	11.7 (8.2)	26.4 (10.7)
Body mass index	25.4 (4.7)	34.2 (8.1)	24.3 (3.4)
Baseline HbA_{1c}	7.5 (1.1)	8.5 (2.1)	7.6 (1.0)
Second HbA_{1c}	7.3 (1.2)	7.9 (1.6)	7.4 (0.8)
Third HbA_{1c}	7.0 (0.9)	7.5 (1.1)	-
# SMBG readings / subject / day	5.4 (2.3)	3.5 (0.8)	4.1 (1.9)
# Days with SMBG readings in the 2 months preceding second HbA_{1c}	56.9 (5.4)	57.3 (4.3)	37.5 (14.3)

OBSERVED METER ERRORS

Our investigation showed that the *major reason for incomplete data* within 60 days prior to HbA_{1c} assays, or elsewhere, was not subject noncompliance, but *meter failure*. The time and date of the One Touch Ultra meter could "jump" to a random date/time (e.g. November 2017), apparently if the patient depressed the "M" button for too long. We were checking the date/time of each meter upon return and we found that such event occurred in 60 meters throughout the course of the study. The time/date shift affected 15,280 readings, or approximately 10% of all readings. We stored these readings separately and had a student review them. In many, but not in all cases he was able to restore the date/time sequence of the readings. This error, together with a few meters lost in the mail, reduced the number of subjects with good data for Algorithm 1 analyses from 179 to 141. The data of 12 subjects were restored, which brought the final count to 153 subjects, 78 with T1DM and 75 with T2DM, who had uninterrupted time sequence of data prior to HbA_{1c}, suitable for testing of Algorithm 1.

PROCEDURE

All subjects signed IRB-approved consent forms and attended orientation meetings where they were introduced to the OneTouch Ultra meter and completed screening questionnaires. Immediately after the introductory meeting all subjects visited a UVA laboratory and had blood drawn for baseline HbA_{1c}. T1DM subjects were followed for 6 months with laboratory HbA_{1c} assays at months 3 and 6; T2DM subjects were followed for 4 months with laboratory HbA_{1c} assays at months 2 and 4. Self-monitoring (SMBG) data were regularly downloaded from the

meters and stored in databases. Parallel recording of significant hypoglycemic and hyperglycemic episodes was done by an automated e-mail/telephone tracking system every two weeks.

DATA STORAGE AND CLEANING

The raw data from OneTouch Ultra were stored in InTouch databases separately for T1DM and T2DM subjects. These raw data were cleaned for subject and meter errors using custom developed software and, in some cases, manual data cleaning (see Meter Errors above). When correction was not possible, the data was discarded.

In order to ensure that the results of our optimization can be generalized to population level, the algorithms were first optimized using a training data set and then validated using test data sets.

The Training Data set included 60 days of SMBG data taken prior to T1DM subjects' 3-month HbA_{1c} determination. This data set was used to optimize the formulas for Algorithm 1. The data of T2DM subjects collected prior to their 2-month HbA_{1c} were used to identify Sample Selection Criteria, which were not apparent in T1DM data. However, T2DM subjects' data were *not used* for optimization of Algorithm 1 formulas. The file containing these data is PASS01.DAT.

Test Data Set 1 included 60 days of SMBG data taken prior to T1DM subjects' 6-month HbA_{1c} determination, and T2DM subjects' 4-month HbA_{1c}. Below we will refer to these data as *Data Set 1*. The file containing these data is PASS02.DAT.

Test Data Set 2 contained data for N=60 subjects with T1DM from a previous NIH study. These data were collected using OneTouch Profile meters. Below we will refer to these data as *Data Set 2*. The file containing these data is HAT0.XLS.

The variables in PASS01.DAT, PASS02.DAT, and HAT0.XLS are as follows:

```
ID, MONTH, DAY, HOUR, YEAR - self-explanatory ID number and time
of reading.
PLASBG - BG as recorded by One Touch Ultra (N/A in HAT0.DAT
because One Touch Profile was used).

RISKLO, RISKHI - control variables representing the result of
data transformation (see below).

BG and BGMM - BG converted to whole blood BG, and then presented
in mmol/l (see below).
```

The aggregated (per subject) data, HbA_{1c}, its estimate, and estimation errors are stored in Excel files PASS1.XLS and PASS2.XLS.

The variables in PASS1.XLS, PASS2.XLS, and HAT1.XLS are as follows:

```
ID, TYPE (of diabetes)

HBA1 - reference baseline HbA1c value

HBA2 - reference HbA1c at 3 months(2 months for T2DM)- this is to
be predicted;

EST2 and ERR2 - Estimate of HbA1c and its error;
```

Control variables (all variables used by Algorithm 1):

```
BGMM1 - average BG in mmol/l (see Part 2 below);

RLO1, RHI1 - low and high BG indices (see Part 2 below);
```

L06 - low BG index at night - computed on readings between midnight and 6:59 a.m. (i.e. if(0.le.HOUR.le.6));

NC1 = number of SMBG readings in the past 60 days;

NDAYS = number of days with SMBG readings in the past 60 days.

N06 - % of SMBG readings in time intervals 0-6:59; 7-12:59;

EXCLUDE = 0,1 - samples suggested for exclusion by the algorithm, if EXCLUDE=1.

The files PASS01.DAT and PASS1.XLS can be matched by subject's ID number. Similarly, files PASS02.DAT and PASS2.XLS and HAT0.XLS and HAT1.XLS can be matched by subject's ID number. The raw data and all second-generation data files were transmitted to LifeScan.

DEVELOPMENT OF ALGORITHM 1

Formula Derivation:

Most of the exploration and the development of Algorithm 1 occurred during Phase 1 of this project (See Phase 1 report from April, 2002). Phase 1 did not include data collection. Instead, we used a data set collected in a clinical trial by Amylin Pharmaceuticals. Phase 1 suggested three possible formulas for estimation of HbA1c from SMBG data: (1) A formula using average SMBG, Low and High BG Indices; (2) A formula using average SMBG and a previous reference HbA1c reading, and (3) A simple linear formula using average SMBG only (see pages 5 and 12 in Phase 1 report).

After presenting to LifeScan the report from Phase 1 in April 2002, the objective of meeting the NGSP criterion for accuracy of HbA_{1c} estimation was set forward (in Phase 1 we used least squares estimation, % error, and absolute error to evaluate the accuracy of each formula). This new requirement translated into a different optimization criterion for Algorithm 1, e.g. the formulas were no longer optimized to produce minimal sum of squares of the errors (least squares estimation), but to fit the estimates within an uniform ± 1 band from reference HbA_{1c}.

In order to do so we analyzed the errors of our first linear model (formula on page 12 in Phase 1 report) with respect to this uniform fit, using *the Training Data for T1DM subjects only*. We found that these errors were positively correlated (r=0.3) with subjects' High BG Index and used this relationship to correct our first linear model. We found that it was best using the High BG Index as a categorical variable, splitting the subject sample into groups with increasing High BG Index, and introducing corrections to the linear model within each group. The idea was to introduce corrections using the Low BG Index within each particular group, not throughout the whole sample as it was suggested in Phase 1 report. This change was dictated by the different scheme of optimization based on the NGSP criterion.

Thus, based on Training Data for T1DM subjects, we finalized the following Algorithm 1:

Part 1 – Pre-Processing of the data:

```
BG=PLASBG/1.12 (converts plasma to whole blood BG, which is used
throughout).
BGMM=BG/18 (converts BG to mmol/l).
```

The following lines compute Low and High BG Index for each SMBG reading:

```
COM SCALE=(ln(BG))**1.08405 - 5.381.
COM RISK1=22.765*SCALE*SCALE.
COM RISKLO=0.
```

```
IF (BG le 112.5) RISKLO=RISK1.
COM RISKHI=0.
IF (BG gt 112.5) RISKHI=RISK1.
```

The following lines aggregate the data per subject:

```
BGMM1 = average (BGMM) per subject;
RLO1 = average (RISKLO) per subject;
RHI1 = average (RISKHI) per subject;
L06 = average (RISKLO) computed only for readings during the night,
     missing if there are no readings at night.
N06, N12, N24 - % of SMBG readings in time intervals 0-6:59; 7-12:59,
     and 18-23:59, e.g. if(0.le.HOUR.le.6)), if(7.le.HOUR.le.12)), and
     if(18.le.HOUR.le.24)), respectively.

NC1 = total number of SMBG readings in the past 60 days;
NDAYS = number of days with SMBG readings in the past 60 days.
```

Part 2 – Estimation Procedure:

This estimation procedure is based on the linear model from our Phase 1 report (page 12):

$$HbA_{1c} = 0.41046*BGMM + 4.0775.$$

Analyzing the errors of this formula we found that the errors depend on the High BG Index. Thus, we classified all subjects on the base of their High BG Index, and then introduced corrections to the linear model within each category as follows:

A. Each subject is assigned a group depending on his/her High BG Index:

```
if (RHI1 le 5.25 or RHI1 ge 16) GRP=0.
if (RHI1 gt 5.25 and RHI1 lt 7.0 ) GRP=1.
if (RHI1 ge 7.0  and RHI1 lt 8.5 ) GRP=2.
if (RHI1 ge 8.5  and RHI1 lt 16) GRP=3.
```

B. For each group we have the following estimates:

```
E0=0.55555*BGMM1+2.95.
E1=0.50567*BGMM1+0.074*L06+2.69.
E2=0.55555*BGMM1-0.074*L06+2.96.
E3=0.44000*BGMM1+0.035*L06+3.65.
     EST2=E0.
     if (GRP eq 1) EST2=E1.
     if (GRP eq 2) EST2=E2.
     if (GRP eq 3) EST2=E3.
```

C. Corrections for some rarely occurring outliers:

```
if (missing(L06)) EST2=E0.
if (RLO1 le 0.5 and RHI1 le 2.0) EST2=E0-0.25.
if (RLO1 le 2.5 and RHI1 gt 26 ) EST2=E0-1.5*RLO1.
if ((RLO1/RHI1) le 0.25 and L06 gt 1.3) EST2=EST2-0.08.
```

ACCURACY CRITERIA

In order to evaluate the accuracy of Algorithm 1 we use several standard criteria:

1) NGSP Accuracy Criterion requires at least 95% of all estimates to be within ±1 HbA_{1c} unit from reference HbA_{1c}.
2) Average absolute deviation of Estimated from measured HbA_{1c};
3) Average percent deviation of Estimated from measured HbA_{1c}.

Important Note: The NGSP accuracy criterion is designed for testing of devices that measure HbA_{1c} directly. Here we apply this criterion to estimates of HbA_{1c} from SMBG data. However, the goal of such estimates is not to replace HbA_{1c} laboratory measurement, it is to *assist patients and physicians* in the day-to-day management of diabetes. As opposed to laboratory measurement, the estimates utilize data that are available anyway and are available on a daily basis, without requiring special equipment or visit at the physician's office.

To illustrate how other direct measures of HbA_{1c} agree with traditional laboratory measures, we tested blood sample from 21 IDDM patients and analyzed for HbA_{1c} with both the DCA 2000 and the clinical laboratory. Out of these 21 tests there was one large error of 2.5 units HbA_{1c}. Table 2 presents the accuracy results of this FDA approved office device:

Table 2: Accuracy of DCA 2000 in T1DM:

	DCA 2000
NGSP criterion - % within ±1 HbA_{1c} unit	95.2%
Average absolute error (units HbA_{1c})	0.45
Average percent error	5.7%

SAMPLE SELECTION CRITERIA

Formula Derivation:

The estimation of HBA1c uses 60 consecutive days of SMBG. We will refer to such 60 consecutive days of SMBG as *sample*. Each person generates numerous samples in the course of his/her SMBG. In fact, each new measurement brings about a new sample, slightly different than the previous one. Thus, it is a natural assumption that the meter should have some control points for the quality of SMBG sample data from which HbA_{1c} is to be estimated.

Therefore, after the general algorithm formula was optimized, it was then applied to the entire Training Data Set (data for T1DM and T2DM subjects) in order to investigate conditions under which a SMBG sample would result in an inaccurate estimation of HbA_{1c}.

This investigation concentrated on the following patterns occurring in SMBG that would result in inaccurate estimation:

1) Infrequent SMBG – certain number of reading is needed over two months in order to estimate HbA1c. If this number is not achieved, the estimation maybe inaccurate;
2) Patterns of SMBG skewed towards hyperglycemia occurring when subjects test predominantly after meals, or use oral medications with a primary concern of high BG;
3) Skewed temporal patterns of SMBG, e.g. testing predominantly at a few fixed times each day, which does not yield a good daily profile of a subject's BG fluctuations.

After investigating such patterns, we selected optimal sample selection criteria based on the most accurate and least exclusionary cut points. For a detailed description of the programming logic and statements for coding purposes please refer to Appendix A.

Final Sample Selection Criteria:

Criterion 1. Test Frequency: The algorithm will require that a 60-day sample contain an average of at least 2.5 tests per day, e.g. at least 150 SMBG readings over the last 60 days to generate an HbA1c estimate (`NC1 >=150`).

Criterion 2. Randomness of Data:

2a) *Oral Therapy / Postprandial Testing:* (`RLO1/RHI1 >=0.005`). In some SMBG samples the distribution of SMBG appeared to be very skewed towards hyperglycemia. This happened predominantly in T2DM subjects, who appeared to measure only at high BG. We have hypothesized that these samples contained no testing at low glucose ranges. Our investigation showed that about 1/3rd of such samples would result in an overestimate of HbA_{1c} (2/3^{rds} would still result in accurate estimates). Based on that we recommend the meter to display no results, if a skewed sample is encountered, which in terms of computation is formulated as LBGI to be at least ½% of the HBGI.

2b) *Testing during the night:* (`NO6 >=3%`). This criterion ensures that at least some of nighttime glycemia is accounted for. This criterion requires that 3% of all the readings occur at night (between midnight and 7:00 am). *In other words*, a sample will be acceptable if *at least 5 out of 150 readings*, taken over 2 months, are during the night. Note that patients are often advised to test at night, so this criterion promotes good management.

Accuracy in the Training Data Set with Sequentially Employed Sample Selection:

The following tables describe the impact of the selected sample selection criteria on the accuracy and number of exclusions in the Training Data Set. Note that the accuracy of the final version of Algorithm 1 developed as a part of this study (Final Algorithm), and the accuracy of the simplest linear function that has been developed in Phase 1 and included in the Phase 1 report, page 12 (First Linear Model).

For each model we present its accuracy without any sample selection criteria and with sequentially applied sample selection Criterion 1 - Test Frequency, # readings NR≥150, and Criterion 2 - Randomness of Data, as described above.

As seen in all tables, the accuracy of Algorithm 1 improves with sequentially applied sample selection criteria and reaches the NGSP required 95% after applying all criteria. These latter results are highlighted in the tables.

[redacted]

Table 3a: Final Sample Selection Criteria in Training Data Set – all subjects:

	Final Algorithm			First Linear Model		
	No sample exclusion	Criterion 1	Criteria 1 and 2	No sample exclusion	Criterion 1	Criteria 1 and 2
NGSP criterion - % within ±1 HbA_{1c} unit	93%	93%	95.5%	83%	83%	90%
Average absolute error (units HbA_{1c})	0.54	0.53	0.47	0.61	0.59	0.52
Average percent error	7.2%	7.2%	6.8%	8.2%	8.2%	7.6%
# of subjects with absolute error > 1	11	9	5	26	22	11

Table 3b: Final Sample Selection Criteria in Training Data Set – T1DM: The coefficients of Algorithm 1 were optimized in this sample, which explains the high accuracy even without sample selection.

	Final Algorithm			First Linear Model		
	No sample exclusion	Criterion 1	Criteria 1 and 2	No sample exclusion	Criterion 1	Criteria 1 and 2
NGSP criterion - % within ±1 HbA_{1c} unit	96%	96%	96%	86%	88%	90%
Average absolute error (units HbA_{1c})	0.45	0.46	0.45	0.54	0.53	0.51
Average percent error	6.3%	6.6%	6.5%	7.7%	7.8%	7.6%

Table 3c: Final Sample Selection Criteria in Training Data Set - T2DM: The Sample Selection Criterion 2 (Randomness of data) was developed primarily using this sample, which explains the 5% increase in accuracy when this criterion is applied.

	Final Algorithm			First Linear Model		
	No sample exclusion	Criterion 1	Criteria 1 and 2	No sample exclusion	Criterion 1	Criteria 1 and 2
NGSP criterion - % within ±1 HbA_{1c} unit	89%	90%	95%	80%	79%	91%
Average absolute error (units HbA_{1c})	0.63	0.62	0.52	0.68	0.66	0.53
Average percent error	8.2%	8.0%	7.3%	8.7%	8.5%	7.5%

Frequency of Sample Exclusion in the Training Data:

The meter has a chance of estimating HbA_{1c} at every new reading. If a sample does not meet the selection criteria, then the meter would not display a HbA_{1c} estimate and would:

(a) Wait until an appropriate sample is accumulated, or
(b) If an appropriate sample is not accumulated, e.g. is a person has a permanently skewed measurement pattern, the meter could issue a prompt for SMBG pattern correction.

Our investigation shows that the *majority of subjects (>95%) would get at least 10 HbA_{1c} estimates over 60 days (as long as they measure frequently enough)*, and only 2% of the subjects would get no estimate due to skewed measurement patterns. These 2% of subjects would need to be prompted to correct their measurement pattern. Complete results of this investigation are given below:

We computed how many days (out of 60) a meter would not be able to show HbA_{1c} results to a person due to samples that do not meet the selection criteria:

1) For 72.5% of all subjects the meter will be able to report HbA_{1c} *every day*;
2) For additional 7.5% of all subjects the meter will be able to report HbA_{1c} on 45 to 59 days (out of 60);
3) For additional 10% of all subjects the meter will be able to report HbA_{1c} on 12 to 44 days;
4) For 9 subjects (5.9%) the meter would not be able to report HbA_{1c} unless they change SMBG pattern.

Important Note: Most of these subjects would not get an estimate because they did not meet the Test Frequency Criterion 1, e.g. their samples always had less than 150 readings. Therefore, at least 94% of all subject will get at least one HbA_{1c} estimate about every 5 days without changing their measurement pattern (this includes T1DM and T2DM).

If we require at least 150 readings for 60 days, only 3 subjects would not get HbA_{1c} estimate:

1) 95.6% will get at least 10 HbA_{1c} estimates over 60 days;
2) 2.2% will not get any estimates.

Thus, approximately *98% of the subjects who measure on average 2.5 times a day will get HbA_{1c}* estimate over 60 days, > 95% will get estimate at least once a week. We conclude that the Sample Selection Criterion 2 - Randomness of Data has, over time, a minimal impact on the display of HbA_{1c} estimates. Only about 2% of the subjects would need to be prompted to improve their SMBG pattern.

It should be noted that the sample selection criteria are applicable to improve the accuracy of *any formula estimating HbA_{1c}*. The selection criteria are independent from any particular algorithm/formula and are applied before the estimation begins. For example, when applied, the sample selection criteria improve the accuracy of the latest Algorithm 1 developed as part of this study, *and* the accuracy of our first linear model presented in the report from Phase 1.

In addition, examining the effect of some other sample selection criteria reveals ways we can improve the accuracy further, should that be desirable. For example, when one of the original test frequency criteria was applied to the data, it demonstrated some incremental utility. This criterion is described further in Appendix E.

PROSPECTIVE VALIDATION OF ALGORITHM 1:

Accuracy in Test Data Set 1:

The algorithm, including the final sample selection criteria, was then applied to Test Data Set 1 (SMBG for two months prior to last HbA_{1c} for T1DM 1 and T2DM subjects) to generate HbA_{1c} estimates. These estimates were then compared to reference HbA_{1c} in order to prospectively validate Algorithm 1. Table 4 presents a summary of the results of this validation. A more detailed account of the impact of each of the sample selection criteria on the accuracy of the algorithm and can be found in Appendix C.

Table 4: Accuracy of Algorithm 1 Applied Prospectively:

	Final Algorithm with Criteria 1 and 2		
	All Subjects	**T1DM**	**T2DM**
NGSP criterion - % within ±1 HbA_{1c} unit	95.1%	97%	93%
Average absolute error (units HbA_{1c})	0.45	0.38	0.54
Average percent error	6.2%	5.4%	7.4%

Accuracy in Test Data Set 2:

Another independent NIH data set (N=60 subjects with T1DM) was used to validate the results with similar accuracy of 95.5% within 1 HbA_{1c} percent units of the lab reference (Table 5):

Table 5: Accuracy of Algorithm 1 in Independent NIH Data Set:

	Final Algorithm			First Linear Model		
	No sample exclusion	**Criterion 1**	**Criteria 1 and 2**	**No sample exclusion**	**Criterion 1**	**Criteria 1 and 2**
NGSP criterion - % within ±1 HbA_{1c} unit	87%	92%	95.5%	88%	92%	91%
Average absolute error (units HbA_{1c})	0.61	0.47	0.42	0.60	0.49	0.46
Average percent error	8.4%	6.5%	5.9%	8.4%	6.8%	6.6%
# of subjects with absolute error > 1	8	2	1	7	2	2

Comparison of Accuracy of Algorithm 1 to FDA-approved Office Device:

As shown in Table 6 below, the accuracy of Algorithm 1 is comparable to the accuracy of HbA1c assays used in physicians' offices. As described in the Accuracy Criteria section, the DCA 2000 data was taken to illustrate how other direct measures of HbA_{1c} agree with laboratory measures. We analyzed for HbA_{1c} blood samples from 21 T1DM patients with both the DCA 2000 and the clinical laboratory. Out of these 21 tests there was one large error of 2.5 units HbA_{1c}. Table 6 compares the accuracy results of this FDA approved office device to Algorithm 1:

Table 6: Accuracy of DCA 2000 in T1DM compared to Algorithm 1:

	DCA 2000	**TEST DATA SET 1**	**TEST DATA SET 2**
NGSP criterion - % within ±1 HbA_{1c} unit	95.2%	95.1%	95.5%
Average absolute error (units HbA_{1c})	0.45	0.45	0.42
Average percent error	5.7%	6.2%	5.9%

Frequency of Sample Exclusion in the Test Data:

As we discussed as part of the development of Algorithm 1, the meter has a chance of estimating HbA_{1c} at every new reading. If a sample does not meet the selection criteria, then the meter would not display a HbA_{1c}.

We used Test Data Sets 1 and 2 to prospectively estimate the frequency of sample exclusion. In order to do so, we computed on how many days (out of 60) a meter would be able to show HbA_{1c} results to a person, e.g. on how many days a person would have samples meeting the sample selection criteria. Tables 7A and 7B present summaries of these results for Test Data Sets 1 and 2. We include data for all subjects, and separately for subjects who measured on average 1.5 times/day (90 SMBG readings over 60 days) and 2.5 times/day (150 SMBG readings over 60 days):

Table 7A: Frequency of Sample Exclusion in Test Data Set 1:

	All subjects (N=148)	Subjects who measured on average ≥ 1.5 times/ day (N=146)	Subjects who measured on average ≥ 2.5 times/ day (N=130)
Percent of subjects to whom the meter will be able to report HbA_{1c} *every day*;	69.6%	72.6%	77.7%
Percent of subjects to whom the meter will be able to report HbA_{1c} *once every 3 days*;	87.8%	91.1%	93.1%
Percent of subjects to whom the meter will be able to report HbA_{1c} *once a week*;	91.9%	95.5%	96.9%

Table 7B: Frequency of Sample Exclusion in Test Data Set 2:

	All subjects (N=60)	Subjects who measured on average ≥ 1.5 times/ day (N=55)	Subjects who measured on average ≥ 2.5 times/ day (N=30)
Percent of subjects to whom the meter will be able to report HbA_{1c} *every day*;	51.7%	83.6%	80.0%
Percent of subjects to whom the meter will be able to report HbA_{1c} *once every 3 days*;	95.0%	100.0%	100.0%
Percent of subjects to whom the meter will be able to report HbA_{1c} *once a week*;	96.7%	100.0%	100.0%

Conclusion:

Tables 4 through 7 demonstrate that the meter would be able to produce an accurate estimate of HbA_{1c}, meeting the 95% NGSP accuracy criterion, at least once a week for > 95% of all subjects, even if subjects tend to measure on average only 1.5 times per day.

APPENDIX A - SOFTWARE LOGIC FOR SAMPLE SELECTION CRITERIA

Sample Selection Criteria – some SMBG samples are suggested for exclusion by the algorithm, or a message is issued to the subjects to correct their SMBG pattern. The sample selection criteria are programmed as follows:

Criterion 1. Test Frequency: The algorithm will require that a 60-day sample contain an average of at least 2.5 tests per day, e.g. at least 150 SMBG readings over the last 60 days to generate an HbA_{1c} estimate:

```
EXCLUDE=0.
if (NC1 >=150) EXCLUDE=1.
```

Criterion 2. Randomness of Data:

2a) *Oral Therapy / Postprandial Testing:* In some SMBG samples the distribution of SMBG appeared to be very skewed towards hyperglycemia. This happened predominantly in T2DM subjects, who appeared to measure only at high BG. We have hypothesized that these samples contained no testing at low glucose ranges. Our investigation showed that about 1/3rd of such samples would result in an overestimate of HbA_{1c} (2/3rds would still result in accurate estimates). Based on that we recommend the meter to display no results, if a skewed sample is encountered, which in terms of computation is formulated as LBGI to be at least ½% of the HBGI.

```
if (RLO1/RHI1 lt 0.005) EXCLUDE=1.
```

2b) *Testing during the night:* (NO6 >=3%). This criterion ensures that at least some of nighttime glycemia is accounted for. This criterion requires that 3% of all the readings occur at night (between midnight and 7:00 am). *In other words*, a sample will be acceptable if *at least 5 out of 150 readings*, taken over 2 months, are during the night. Note that patients are often advised to test at night, so this criterion promotes good management.

```
if (NO6 le 3.0) EXCLUDE=1.
```

APPENDIX B -

APPENDIX C - INCREMENTAL EFFECT OF SAMPLE SELECTION CRITERIA ON ACCURACY OF ALGORITHM 1 IN TEST DATA SET 1

As described in the development of the algorithm, the following tables refer to Algorithm 1 developed as a part of this study (Final Algorithm), and the accuracy of the simplest linear function that has been developed in Phase 1 and included in the Phase 1 report, page 12 (First Linear Model). The tables present the accuracy of Algorithm 1 in Test Data Set 1 without sample exclusion and with sequential application of the two sample selection criteria:

Criterion 1 - Test Frequency, # readings NR≥150, and

Criterion 2 - Randomness of Data, as described under Sample Selection Criteria:

Table 8a: Accuracy of Algorithm – all subjects:

	Final Algorithm			First Linear Model		
	No sample exclusion	Criterion 1	Criteria 1 and 2	No sample exclusion	Criterion 1	Criteria 1 and 2
NGSP criterion - % within ±1 HbA_{1c} unit	86%	91%	95.1%	83%	85%	89%
Average absolute error (units HbA_{1c})	0.56	0.48	0.45	0.59	0.54	0.49
Average percent error	7.4%	6.7%	6.2%	7.8%	7.5%	7.0%
# of subjects with absolute error > 1	21	10	5	25	16	11

Table 8b: Accuracy of Algorithm 1 in T1DM:

	Final Algorithm			First Linear Model		
	No sample exclusion	Criterion 1	Criteria 1 and 2	No sample exclusion	Criterion 1	Criteria 1 and 2
NGSP criterion - % within ±1 HbA_{1c} unit	90%	95%	97%	90%	93%	95%
Average absolute error (units HbA_{1c})	0.45	0.40	0.38	0.49	0.45	0.43
Average percent error	6.1%	5.6%	5.4%	6.9%	6.7%	6.4%

Table 8c: Accuracy of Algorithm 1 in T2DM:

	Final Algorithm			First Linear Model		
	No sample exclusion	Criterion 1	Criteria 1 and 2	No sample exclusion	Criterion 1	Criteria 1 and 2
NGSP criterion - % within ±1 HbA_{1c} unit	81%	86%	93%	76%	76%	81%
Average absolute error (units HbA_{1c})	0.68	0.59	0.54	0.69	0.64	0.57
Average percent error	8.6%	8.0%	7.4%	8.7%	8.6%	7.8%

APPENDIX D - ALTERNATIVE TESTING FREQUENCY CRITERION

A superior Testing Frequency criterion may contribute more significantly to the accuracy of Algorithm 1. This is because reasons for employing the Testing Frequency Criterion 1 were based not solely on data analysis, but on other considerations. If Criterion 1 requiring 150 readings in 2 months is found too restrictive, an alternative solution maybe used. This is the original Testing Frequency criterion, which required 35 days (out of 60) with SMBG readings with an average frequency of 1.8 readings/day, e.g. a total of 63 readings taken over 35 out of 60 days. Table 9 demonstrates that with this original relaxed testing frequency criterion, plus Criterion 2 (randomness of data), the accuracy of Algorithm 1 exceeds 95%:

Table 9: Accuracy of Algorithm 1 using alternative Testing Frequency Criterion (35 of readings/1.8 readings/day) and the Randomness of Data Criterion:

	Training Data Set			Test Data Set 1			Test Data Set 2
	All Ss	T1DM	T2DM	All Ss	T1DM	T2DM	
NGSP criterion - % within +1 HbA_{1c} unit	95%	96%	94%	95%	97%	92%	100%
Average absolute error (units HbA_{1c})	0.48	0.44	0.55	0.46	0.39	0.55	0.40
Average percent error	6.8%	6.3%	7.6%	6.3%	5.5%	7.2%	5.5%

Important Note: In addition, this alternative criterion screens out samples, which have big chunk of missing data, e.g. if SMBG was discontinued for 4 weeks and then the person comes back, HbA_{1c} estimate should not be displayed. A clear example of such a pattern occurred in Test Data Set 2 – the subject who had the largest error in his/her HbA_{1c} estimate had collected 159 readings over only 30 out of 60 days. Thus, it is possible for a subject to meet the requirement of 150 readings with readings collected quickly over a few days, which may result in inaccurate HbA1c estimation.

00543-20

METHOD, SYSTEM, AND COMPUTER PROGRAM PRODUCT
FOR PROCESSING OF SELF-MONITORING BLOOD GLUCOSE (SMBG) DATA TO ENHANCE DIABETIC SELF-MANAGEMENT

REPORT OF FINDINGS FROM PHASE 2 – PART 2:

Algorithm 2: Evaluation of Long-Term Risk For Significant Hypoglycemia

Algorithm 3: Prediction of Upcoming (within 24 hours) Significant Hypoglycemia

Table of Contents:

DEFINITIONS

1) Severe hypoglycemia (SH) is identified as low blood glucose (BG) resulting in stupor, seizure, or unconsciousness that precludes self-treatment;
2) Moderate hypoglycemia (MH) is identified as severe neuroglycopenia disrupting subject's activity, but not precluding self-treatment;
3) Biochemical severe hypoglycemia (BSH) is defined as plasma BG reading <= 39 mg/dl;
4) Biochemical moderate hypoglycemia (BMH) is defines as plasma BG reading between 39 and 55 mg/dl.
5) All of the above will be referred to as *significant hypoglycemia*.

OBJECTIVES

The data from Phase 2 were used to validate prospectively the following algorithms:

Algorithm 2 - a classification algorithm using 30-45 days of SMBG data for a subject, to classify this subject in a certain risk category for future significant hypoglycemia. The classification is temporary, e.g. when a subjects' SMBG pattern changes, the classification changes as well;

Algorithm 3 - a data tracking/decision-making algorithm that uses a sequence of SMBG data to make a decision whether to raise a flag for upcoming (within 24 hours) significant hypoglycemia.
We now describe in detail Algorithms 1&2 and the results of their testing.

[redacted]

SUBJECTS

We have consented 100 subjects with Type 1 Diabetes (T1DM) and 100 subjects with Type 2 Diabetes (T2DM). One hundred seventy-nine subjects, 90 with T1DM and 89 with T2DM, completed significant portions of the SMBG data collection.

PROCEDURE

All subjects signed an IRB—approved consent forms and attended orientation meetings where they were introduced to the OneTouch Ultra meter and completed screening questionnaires. Immediately after the introductory meeting all subjects visited a UVA laboratory and had blood drawn for baseline HbA_{1c}. T1DM subjects were followed for 6 months with laboratory HbA_{1c} assays at months 3 and 6; T2DM subjects were followed for 4 months with laboratory HbA_{1c} assays at months 2 and 4. Self-monitoring (SMBG) data were regularly downloaded from the meters and stored in databases. Parallel recording of significant hypoglycemic and hyperglycemic episodes was done by a custom-designed automated e-mail/telephone tracking system contacting all participants in two-week intervals. Table 1 present summaries of the SMBG and Severe Hypoglycemia Moderate Hypoglycemia [SH/MH] data collection.

Table 1: Data collection summary

Variable	**T1DM** (N=90 subjects)	**T2DM** (N=89 subjects)
# SH episodes	88	24
# MH episodes	1,660	190
# SMBG readings	92,737	35,306
# BSH episodes	1,039	39
# BMH episodes	5,179	283

No significant changes were made to the formulas of Algorithms 2 and 3. These formulas remain practically identical to the formulas presented in the report from Phase 1 of March 2002. The only two changes include: (a) a correction of a typo in the list of risk categories for SH/MH (page 14 of Phase 1 report) and (b) change in one line of Algorithm 3 (page 28 of Phase 1 report). The reason for the latter is explained below.

Since Algorithms 1 and 2 remain unchanged, we can consider the entire Phase 2 data collection as a prospective testing of these algorithms.

FORMULAS for ALGORITHM 2

Algorithm 2 proceeds as follows:

1) Based on one month of SMBG data, each subject is classified into one of 15 risk categories (RCAT) depending on his/her Low BG Index (LBGI) as follows:

```
if (LBGI le 0.25) RCAT=0.
if (LBGI gt 0.25 and LBGI le 0.50) RCAT=1.
if (LBGI gt 0.50 and LBGI le 0.75) RCAT=2.
if (LBGI gt 0.75 and LBGI le 1.00) RCAT=3.
if (LBGI gt 1.00 and LBGI le 1.25) RCAT=4.
if (LBGI gt 1.25 and LBGI le 1.50) RCAT=5.
```

```
if (LBGI gt 1.50 and LBGI le 1.75) RCAT=6.
if (LBGI gt 1.75 and LBGI le 2.00) RCAT=7.
if (LBGI gt 2.00 and LBGI le 2.50) RCAT=8.
if (LBGI gt 2.50 and LBGI le 3.00) RCAT=9.
if (LBGI gt 3.00 and LBGI le 3.50) RCAT=10.
if (LBGI gt 3.50 and LBGI le 4.25) RCAT=11.
if (LBGI gt 4.25 and LBGI le 5.00) RCAT=12.
if (LBGI gt 5.00 and LBGI le 6.50) RCAT=13.
if (LBGI gt 6.50) RCAT=14.
```

2) The theoretical probability for future significant hypoglycemia are computed through a two-parameter Weibull probability distribution, with a distribution function given by the formula: $F(x) = 1 - exp(-a.x^b)$ for any $x>0$ and 0 otherwise. The parameters of this distribution depend on the desired duration of the prediction and are described in the report from Phase 1. If implemented in a meter, this step would provide a continuous-type estimation of the risk for significant hypoglycemia, e.g. "50% within the next month."

3) Each subject is classified at minimal, low, moderate, or high risk for future significant hypoglycemia: These ranges are defined as follows: Minimal risk (LBGI≤1.25); Low risk (1.25<LBGI≤2.5); Moderate risk (2.5<LBGI≤5), and High risk (LBGI>5). If implemented in a meter, this step would provide a discrete-type estimation of the risk for significant hypoglycemia, e.g. "high risk within the next month."

FORMULAS for ALGORITHM 3

First, in order to avoid the computing of baseline risk values presented in the Phase 1 Report description of Algorithm 3, we have modified one line in the code. Now Algorithm 3 uses the results from Algorithm 2 instead. This change was introduced for the presentation of sample results for two subjects on October 28, 2002. At this time it appeared that it was more convenient to have a simple Excel spreadsheet to demonstrate the action of Algorithm 3, iwhich was possible if the computation of baseline values was avoided. This step did not change the accuracy of Algorithm 3 and therefore was left as a permanent change facilitating the programming of Algorithm 3. No other changes were introduced to Algorithm 3 after October 28, 2002. Here we present the formulas of Algorithm 3 as given in the report from Phase 1, with the changed line marked.

1) Computing of a Low BG Risk value (RLO) for each BG reading that is done by the following code (here BG is measured in mg/dl, if the units are mmol/l the coefficients are different):

```
scale=(ln(bg))**1.08405 - 5.381
risk=22.765*scale*scale
if (bg_1 le 112.5) then
   RLO=risk
else
   RLO=0
endif
```

2) For each SMBG reading we compute a running value of the LBGI(n), and another statistics, SBGI(n) that is the standard deviation of the low BG risk values. These two parameters were computed with a certain lag (n) backwards from each SMBG reading, e.g. included that reading and (n-1) readings taken prior to that reading.

3) The computation of LBGI(n) and SBGI(n) used a provisional means procedure that is based on the following recursive code:

Initial values at *n* (or at the max(1,n-k) to be exact in order to account for meter readings with a sequential number less than *k*):

```
LBGI(n)=rlo(n)
rlo2(n)=0
```

Values for any consecutive iteration *j* between *n* and *1*, counted backwards:

```
LBGI(j)=((j-1)/j)*LBGI(j-1) + (1/j)*RLO(j)
rlo2(j)=((j-1)/j)*rlo2(j-1) + (1/j)*(RLO(j)-LBGI(j))**2
```

After this cycle is completed we have the value of LBGI(n) and we compute

```
SBGI(n)=sqrt(rlo2(n))
```

From this computation we save two sets of values: for *n=150* and for *n=50* (e.g. for the last 150 and the last 50 observations).

4) Decision-Making Rule: At each SMBG reading the procedure decides whether to raise a flag warning of upcoming SH. If the flag is raised, the procedure decides whether or not to lower the flag. These decisions depend on three threshold parameters, α, β, γ that work as follows:

For subject at low-to-moderate risk (LM group):

```
FLAG=0.
if(LBGI(150) ge 2.5 and LBGI(50) ge (1.5*LBGI(150) and SBGI(50) ge SBGI(150))
FLAG=1.
if (RLO ge (LBGI(150)+1.5*SBGI(150)) FLAG=1.
```

In other words, at each SMBG reading the flag could be raised if one of two conditions is met:

1) The subject to be at a moderate of high risk for SH based on Algorithm 2 classification from the last 150 trials and the LBGI and SD of LBGI to increase over the last 50 trials;

2) Or, to have a surge in the Low BG Index as determined by the second inequality.

The heuristic explanation of these statements was presented in the report from Phase 1. As described above the first "if" statement has been changed from its original form to avoid the use of baseline LBGI and to utilize the output from Algorithm 2.

As described in the report from Phase 1, once the flag is raised it remains raised for 24 hours. In order to evaluate the accuracy of Algorithm 3 we use the technique proposed before – we compute two measures:

1) The % predicted upcoming SH/MH episodes within 24 hours, and

2) The ratio R_{ud} of duration periods of "flag up" to "flag down" (annoyance index).

While the % predicted episodes of SH needs to be high, the ratio R_{ud} needs to be low. This is because by increasing the percentage of predicted SH episodes, we unavoidably increases the number of "raised flags," which in turn increases the number of potential "false alarms." Since a "false alarm" is not clearly defined (see report from Phase 1), we will use R_{ud} as an indicator of the utility of Algorithm 3.

Our previous best result presented in the report from Phase 1 was a prediction of 50% of SH/MH episodes within 24 hours, and R_{ud}=1:10, e.g. one day of high-risk alert was alternating with 10 days of no alert. Here we will keep the same flag up/down ratio and will compute the % predicted within 24 hours SH and MH episodes separately for T1DM and T2DM subjects. For this prediction we will not use BSH and BMH episodes since these were recorded by the meter and therefore are a part of the prediction function.

EVALUATION OF RISK FOR SIGNIFICANT HYPOGLYCEMIA WITHIN 1-3 MONTHS: ACCURACY OF ALGORITHM 2

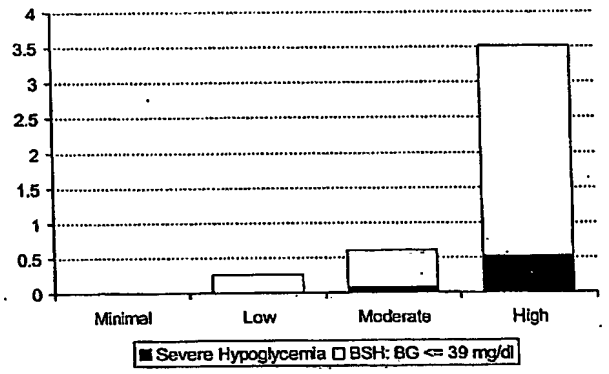
We have evaluated the predictive power of Algorithm 2 as follows:

1) First, we have computed the LBGI from one month of SMBG data and classified each subject at Minimal, Low, Moderate, and High risk for significant hypoglycemia as described above.
2) Then, during the following 1-3 months we counted for each subject the number of prospectively recorded SH, BSH, MH, and BMH episodes.

The figures below present the number of SH, BSH, MH, and BMH episodes per subject observed prospectively for 1 month, or 3 months, following a month of SMBG, separately for T1DM and T2DM. Statistical comparisons are included as well:

Figure 1: One-month Risk for Significant Hypoglycemia in T1DM Predicted by the LBGI

ANOVA of number of severe hypoglycemic episodes by Risk Group: F=7.2, p<0.001
ANOVA of number of moderate hypoglycemic episodes by Risk Group: F=13.9, p<0.001



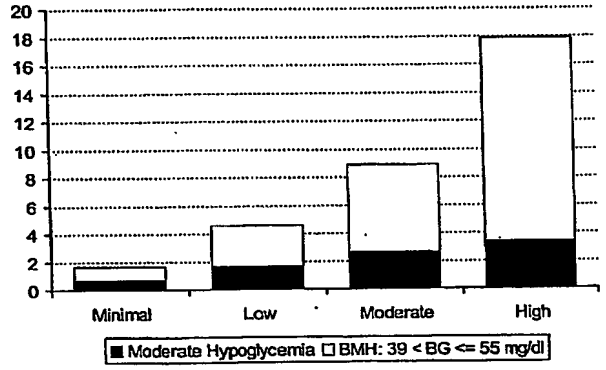
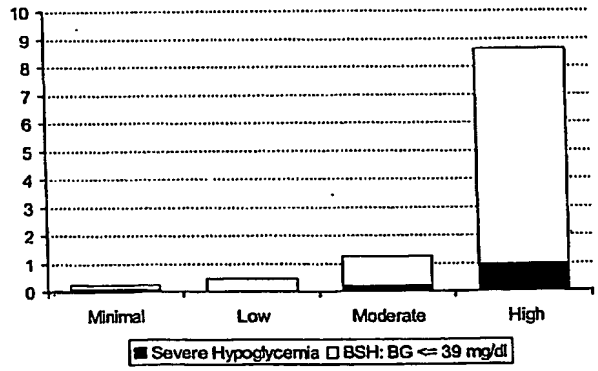


Figure 2: 3-month Risk for Significant Hypoglycemia in T1DM Predicted by the LBGI

ANOVA of number of severe hypoglycemic episodes by Risk Group: F=9.2, p<0.001
ANOVA of number of moderate hypoglycemic episodes by Risk Group: F=14.7, p<0.001



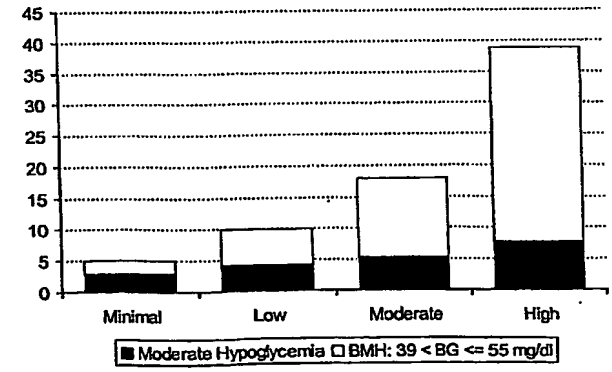


Figure 3: One-month Risk for Significant Hypoglycemia in T2DM Predicted by the LBGI

ANOVA of number of severe hypoglycemic episodes by Risk Group: F=6.0, p<0.005
ANOVA of number of moderate hypoglycemic episodes by Risk Group: F=25.1, p<0.001

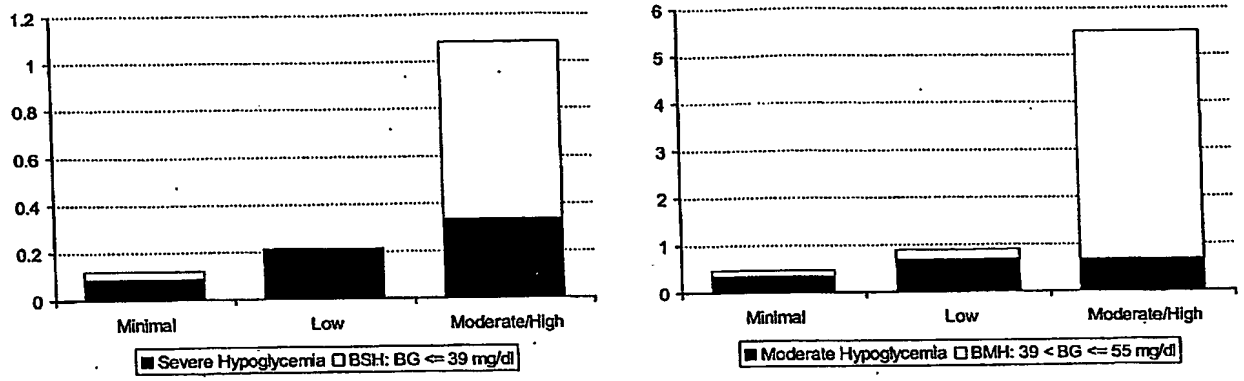
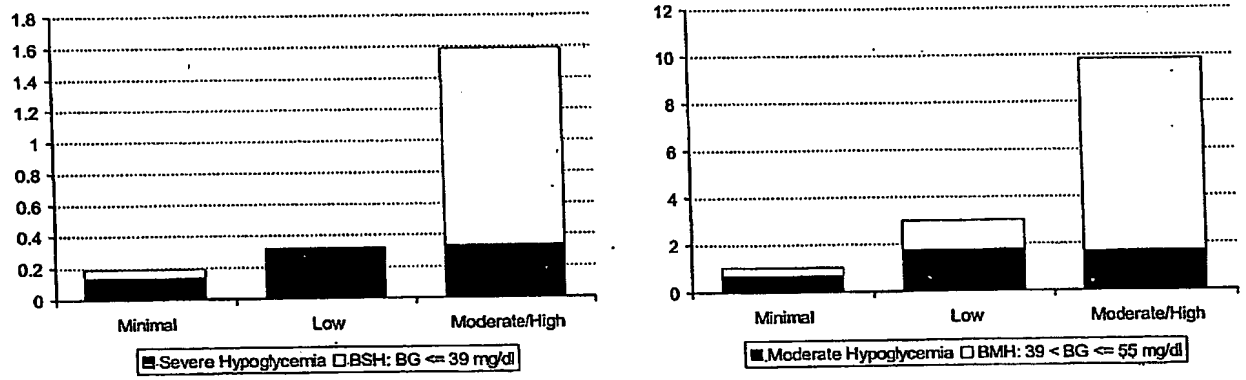


Figure 4: 3-month Risk for Significant Hypoglycemia in T2DM Predicted by the LBGI

ANOVA of number of severe hypoglycemic episodes by Risk Group: F=5.3, p<0.01
ANOVA of number of moderate hypoglycemic episodes by Risk Group: F=20.1, p<0.001



In addition, a *direct linear regression* using the LBGI, history of SH as reported in the screening questionnaires in terms of number of episodes in the past year, and baseline HBA_{1c}, predicted significantly (R^2=0.62, F=48, p<0.0001) the total number of upcoming in the next 3 months significant hypoglycemic episodes (SH+MH+BSH+BMH). The predictive variables, in order of their significance were: 1) LBGI (t=8.2, p<0.0001) accounting alone for 55% of the variance of future significant hypoglycemia (e.g. R^2=0.55); 2) History of SH (t=3.6, p=0.0005) accounting for additional 5% variance, and HbA1c (t=2.2, p=0.03) accounting for additional 2% variance. This confirms previous results that the LBGI is a most significant predictor of future hypoglycemia, while the contribution of HbA_{1c} to that prediction is modest.

The *theoretical probabilities* for future significant hypoglycemia computed by the Weibull model had an excellent agreement with the prospectively observed significant hypoglycemic episodes – for both severe and moderate episodes the coefficients of determination were above 90%.

PREDICTION OF UPCOMING (WITHIN 24 HOURS) SIGNIFICANT HYPOGLYCEMIA: ACCURACY OF ALGORITHM 3

The tables below present the accuracy of the short-term prediction (within 24 hours) of SH and MH episodes separately for T1DM and T2DM subjects. Each line of Tables 2 and 3 presents the percent predicted episodes, if a certain number of SMBG readings were available in the 24-hour period used for the prediction. For example, the first line in each table presents the % predicted episodes regardless of whether there were any SMBG readings in the 24 hours preceding an episode. It is seen that the accuracy of the prediction increases with the number of readings preceding an episode. *Thus, if a person measures 3 or more times a day, the meter could warn about, and potentially help avoid, more than half of significant hypoglycemic episodes.*

Important Note: For the purposes of accuracy assessment of Algorithm 3 we use only SH and MH episodes recorded by the independent from SMBG e-mail/telephone system, which required each participant to report SH and MH by date and time every two weeks. As our interviews showed, sometimes the participants used for their reports the time and date of the last SMBG reading preceding an episode, instead of the actual time/date of that episode, because looking at the meter was helping their recollection. As a result, there were a number of episodes for which the time elapsed from the closest preceding SMBG reading to the time of the episode, was close to zero. In order to account for such suspicious time recording Column 3 in each table presents the accuracy of Algorithm 3 restricted only to episodes for which the lead warning time was *at least 15 minutes*. Given that the average lead warning time was 11 hours, we conclude that in most cases, the warning would come early enough to prompt adequate self-treatment.

In Tables 2 and 3 the Annoyance Index is set to R_{ud} >=10 to match the report from Phase 1.

Table 2: Accuracy of Algorithm 3 in T1DM.

R_{ud} = 10.2		% Predicted **SH+MH** Episodes	% Predicted **SH** Episodes	% Predicted **SH+MH** Episodes with warning time > 15 minutes
No restrictions		53%	48%	49%
Minimum number of SMBG readings in the 24 hours preceding the episode.	3	55%	58%	52%
	4	59%	60%	55%
	5	63%	60%	59%

Table 3: Accuracy of Algorithm 3 in T2DM.

R_{ud} = 10.0		% Predicted **SH+MH** Episodes	% Predicted **SH** Episodes	% Predicted **SH+MH** Episodes with warning time > 15 minutes
No restrictions		52%	38%	48%
Minimum number of SMBG readings in the 24 hours preceding the episode.	3	57%	60%	53%
	4	64%	64%	59%
	5	73%	73%	68%